Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome–positive leukemias. N Engl J Med 2013;369:1783-96. DOI: 10.1056/NEJMoa1306494

APPENDICES, SUPPLEMENTAL TABLES, SUPPLEMENTAL FIGURE

Ponatinib in Refractory Ph-Positive Leukemias: A Phase 2 Trial

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Appendix A. List of PACE (Ponatinib Ph+ ALL and CML Evaluation) Investigators

The following were investigators in the PACE clinical trial:

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Appendix B. Protocol Summary: Phase 2 Study of Ponatinib - Protocol AP24534-10-201

Objectives

Primary objective:

To determine the efficacy of ponatinib in patients with CML in chronic, accelerated or blast phase or with Ph+ ALL who are either:

- resistant or intolerant to either dasatinib or nilotinib,

or

- have the BCR-ABLT315I mutation.

Secondary objectives:

1. To further characterize the anti-leukemia activity of ponatinib in these patients as evidenced by clinical responses, molecular responses, and clinical outcomes;
2. To characterize the molecular genetic status of patients; and
3. To examine the safety of ponatinib in these patients.

Design

This is an ongoing multi-center, international, phase 2, single-arm, open-label trial of oral ponatinib in patients with Ph+ disease. Eligible patients have CML in CP, AP, or BP, or Ph+ ALL. Patients either 1) have disease resistant to, or are intolerant to, therapy with either dasatinib or nilotinib; or 2) have the T315I mutation of BCR-ABL. Patients receive once daily oral administration of ponatinib tablet at a dose of 45 mg. Patients are assessed for hematologic response, cytogenetic response, and molecular response. Molecular genetic analyses are also being performed. Adverse events are being assessed throughout and categorized by NCI CTCAE v. 4.0. Assessments are according to standard international criteria. Patients will remain on treatment until disease progression or intolerance develops. Progression-free survival (PFS) and overall survival data are being collected and analyzed. Each patient will be followed for up to 24 months after their first dose of ponatinib. If patients remain on therapy after 24 months, patients can remain on ponatinib if continuing to benefit from treatment.

Endpoints

Primary Endpoint:

1. For CML patients in CP at study entry: major cytogenetic response (MCyR), defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR).
    - Patients entering the trial already in PCyR must achieve CCyR in order to be considered as achieving a MCyR.
    - CP patients in CCyR are **not** eligible for this study.
    - Patients not responding by 12 months after the initiation of study treatment will be analyzed as non-responders.
2. For CML patients in AP at study entry: major hematologic response (MaHR), defined as complete hematologic response (CHR) or no evidence of leukemia (NEL).
    - MaHR will be confirmed by a peripheral blood CBC and differential no earlier than 28 days later.
    - Patients not responding by 6 months after the initiation of study treatment will be analyzed as non-responders.
    - AP patients in MaHR are **not** eligible for this study. [**Note**: 14 AP-CML patients with MaHR were enrolled. These patients are analyzed as non-responders in the analysis of MaHR.]
3. For CML patients in BP at study entry or Ph+ ALL patients: MaHR, consisting of CHR or NEL. BP and Ph+ ALL patients in MaHR are **not** eligible for this study.
    - MaHR will be confirmed by a peripheral blood CBC and differential no earlier than 28 days later.

Secondary Endpoints:

1. For CML patients in CP:
    - Hematologic responses: CHR;
    - Cytogenetic responses: confirmed MCyR; and
        - Confirmed MCyR is defined as 2 assessments of CCyR or PCyR at least 28 days apart. For CP patients entering the trial in PCyR, confirmed MCyR will be defined as 2 assessments of CCyR at least 28 days apart.
    - Molecular responses: major molecular response (MMR).
2. For CML patients in AP or BP or Ph+ ALL patients:
    - Cytogenetic responses: CCyR, PCyR, confirmed MCyR; and
        - Confirmed MCyR is defined as 2 assessments of CCyR or PCyR at least 28 days apart.

- Molecular responses: MMR

3. For all patients: time to response, duration of response, progression free survival, and overall survival.
    - Duration of response is defined as the interval between the first assessment at which the criteria for response are met until the criteria for progression are met, censored at the last date at which the criteria for response are met. An additional analysis will be performed defining the duration as the time from the first assessment at which the criteria for response are met until the last assessment at which the criteria for response are met.
    - Progression-free survival is defined as the interval from the first dose of study treatment until the criteria for progression (as defined in Appendix C) or death are met, censored at the last response assessment.
    - Overall survival is defined as the interval from the first dose of study treatment until death, censored at the last date at which patient was known to be alive.
    - Time to response is defined as the interval from the first dose of study treatment until the criteria for response are first met, censored at the last assessment of response.
4. For all patients: safety and tolerability.

Exploratory Endpoints:

1. For all patients: BCR-ABL sequence collection and analysis;
2. For all patients: ASO PCR for T315I (not performed);
3. For all patients: molecular genetic analyses.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Patients must have CML in any phase (CP, AP, or BP of any phenotype) or Ph+ ALL.
    a. All patients must have screening bone marrow (BM) cytogenetics with conventional banding performed within 42 days prior to initiating treatment.
    b. Examination of at least 20 metaphases is required. If less than 20 metaphases are examined, the BM aspirate should be repeated.

Patients must either meet criterion 2 or 3:

2. Be previously treated with and resistant, or intolerant, to either dasatinib or nilotinib:

a. Resistance is defined for CP-CML patients (CP at the time of initiation of dasatinib or nilotinib therapy) as follows. Patients must meet at least 1 criterion.
    i. Three months after the initiation of therapy: No cytogenetic response (>95% Ph+) or failure to achieve CHR.
    ii. Six months after the initiation of therapy: Less than a minor cytogenetic response (>65% Ph+).
    iii. Twelve months after the initiation of therapy: Less than a PCyR (>35% Ph+).
    iv. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of CCyR.
    v. At any time after the initiation of therapy, the development of new clonal evolution in the absence of CCyR.
    vi. At any time after the initiation of therapy, the loss of any cytogenetic response [from complete (0%), partial (1% to 35%), minor (36% to 65%), or minimal (66% to 95%) to a response at least 1 grade worse], confirmed in at least 2 consecutive analyses, separated by at least 4 weeks.
    vii. At any time after the initiation of therapy, progression of disease (to AP or BP).
b. Resistance is defined for AP-CML patients (defined at the time of initiation of dasatinib or nilotinib therapy) as follows. Patients must meet at least 1 criterion.
    i. Three months after the initiation of therapy: failure to achieve a MaHR.
    ii. At any time after the initiation of therapy, the loss of a MaHR, confirmed in at least 2 consecutive analyses, separated by at least 4 weeks.
    iii. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of a MaHR.
c. Resistance is defined for BP-CML patients (defined at the time of initiation of dasatinib or nilotinib therapy) and Ph+ ALL patients as follows. Patients must meet at least 1 criterion.
    i. One month after the initiation of therapy: failure to achieve a MaHR.
    ii. At any time after the initiation of therapy, the loss of a MaHR, confirmed in at least 2 consecutive analyses, separated by at least 1 week.
    iii. At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of a MaHR.

d. Intolerance to dasatinib or nilotinib is defined as:

   i. Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal) in the absence of a CCyR for CP – CML patients or MaHR for AP-CML, BP-CML or Ph+ ALL patients.

   ii. Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer (80 mg QD for dasatinib; 400 mg QD for nilotinib) in the absence of a CCyR for CP-CML patients or MaHR for AP-CML, BP-CML or Ph+ ALL patients.

NOTE: Although the above criteria define failure after dasatinib or nilotinib (mostly according to Baccarani et al[1]), patients who have gone on to later line therapy are eligible having failed dasatinib or nilotinib.

OR

3. Develop the T315I mutation after any TKI therapy.

   a. Patients with T315I mutation after any TKI need not have been treated with dasatinib or nilotinib.

   b. Patients with T315I in CP must have less than a CCyR (>0% Ph+).

   c. Patients with T315I in AP, BP, or Ph+ ALL must have less than a MaHR.

   d. Patients with any history of T315I mutation will be eligible for study participation. However, only those patients who carry a T315I mutation that is detected by direct sequencing in a pre-treatment blood sample using the study's central laboratory will be analyzed in the T315I subset.

Patients must meet all of the remaining criteria to be eligible for the study:

4. Patients must be ≥18 years old.
5. Provide written informed consent.
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
7. Minimum life expectancy of 3 months or more.
8. Adequate renal function defined as serum creatinine < 1.5× upper limit of normal (ULN) for institution.
9. Adequate hepatic function defined as:

   a. Total bilirubin <1.5 × ULN,

   b. Alanine aminotransferase (ALT [SGPT]) and aspartate aminotransferase (AST [SGOT]) < 2.5 × ULN for institution (< 5 x ULN if liver involvement with leukemia),

c. Prothrombin time (PT) < 1.5 × ULN.

10. Normal pancreatic status defined as:
    a. Lipase ≤ 1.5 × ULN for institution
    b. Amylase ≤ 1.5 × ULN for institution
11. Normal QTcF interval on screening ECG evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.
12. For females of childbearing potential, a negative pregnancy test must be documented prior to enrollment.
13. Female and male patients who are of childbearing potential must agree to use an effective form of contraception with their sexual partners throughout participation in this study.
14. Ability to comply with study procedures, in the Investigator's opinion.

Exclusion Criteria:

Patients are not eligible for participation in the study if they meet any of the following exclusion criteria:

1. Received TKI therapy within 7 days prior to receiving the first dose of ponatinib, or have not recovered (> grade 1 by NCI CTCAE, v. 4.0) from AEs (except alopecia) due to agents previously administered.
2. Received other therapies as follows:
    a. For CP and AP patients, received hydroxyurea or anagrelide within 24 hours prior to receiving the first dose of ponatinib, interferon, cytarabine, or immunotherapy within 14 days, or any other cytotoxic chemotherapy, radiotherapy, or investigational therapy within 28 days prior to receiving the first dose of ponatinib.
    b. For BP patients, received chemotherapy within 14 days prior to the first dose of ponatinib. Otherwise 2a applies.
    c. For Ph+ ALL patients, received corticosteroids within 24 hours before the first dose of ponatinib, or vincristine within 7 days prior to the first dose of ponatinib, or received other chemotherapy within 14 days prior to the first dose of ponatinib. Otherwise, 2a applies.
    d. All patients are excluded if they have not recovered (> grade 1 by NCI CTCAE, v. 4.0) from AEs (except alopecia) due to agents previously administered.
3. Underwent autologous or allogeneic stem cell transplant < 60 days prior to receiving the first dose of ponatinib; any evidence of on-going graft-versus-host disease (GVHD), or GVHD requiring immunosuppressive therapy.
4. Take medications that are known to be associated with Torsades de Pointes.
5. Require concurrent treatment with immunosuppressive agents, other than corticosteroids prescribed for a short course of therapy.

6. Have previously been treated with ponatinib.
7. Patients with CML CP are excluded if they are in CCyR.
8. Patients with CML AP, BP, or Ph+ ALL are excluded if they are in MaHR.[**Note**: 14 AP-CML patients had MaHR at baseline. These patients are analyzed as non-responders in the analysis of MaHR.]
9. Have active central nervous system (CNS) disease as evidenced by cytology or pathology. In the absence of clinical CNS disease, lumbar puncture is not required. History itself of CNS involvement is not exclusionary if CNS has been cleared with a documented negative lumbar puncture.
10. Have significant or active cardiovascular disease, specifically including, but not restricted to:
    a. Myocardial infarction within 3 months prior to first dose of ponatinib,
    b. History of clinically significant atrial arrhythmia or any ventricular arrhythmia,
    c. Unstable angina within 3 months prior to first dose of ponatinib,
    d. Congestive heart failure within 3 months prior to first dose of ponatinib.
11. Have a significant bleeding disorder unrelated to CML or Ph+ ALL.
12. Have a history of pancreatitis or alcohol abuse.
13. Have uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
14. Have malabsorption syndrome or other gastrointestinal illness that could affect absorption of orally administered ponatinib.
15. Have been diagnosed with another primary malignancy within the past 3 years (except for non-melanoma skin cancer or cervical cancer in situ, or controlled prostate cancer, which are allowed within 3 years).
16. Are pregnant or lactating. Women of childbearing potential must agree to effective contraception from the time of signing informed consent through the Follow-up Visit, approximately 30 days after last dose of ponatinib.
17. Underwent major surgery (with the exception of minor surgical procedures, such as catheter placement or BM biopsy) within 14 days prior to first dose of ponatinib.
18. Have ongoing or active infection (including known history of human immunodeficiency virus [HIV], hepatitis B virus [HBV], or hepatitis C virus [HCV]). Testing for these viruses is not required in the absence of history.
19. Suffer from any condition or illness that, in the opinion of the Investigator or the medical monitor, would compromise patient safety or interfere with the evaluation of the safety of the study drug.

BCR-ABL Mutation Testing

All patients will undergo testing of the BCR-ABL gene for mutations, regardless of whether a prior mutation analysis has been performed. Testing will be performed on a blood sample obtained during the pre-treatment screening interval. Two tests will be performed. The first will be direct sequencing. This test can detect any mutation in the BCR-ABL kinase domain that is present in at least 20% of transcripts, including the T315I mutation. The second will be ASO quantitative reverse transcript-PCR (ASO qRT-PCR). This is a more sensitive test that detects only the T315I mutation and is being employed as an exploratory assay.

Direct (Sanger) sequencing is the standard test for mutation detection, as was recommended by a panel of experts at an NIH consensus conference in late 2005.[2] Direct sequencing can detect any potential single or compound mutation in BCR-ABL that is present in a sufficient percentage of transcripts.[3] Patients who demonstrate the T315I mutation by this assay, irrespective of prior treatments, will be included in one of the T315I cohorts (depending on their stage of disease) for analysis. T315I patients, and thus the T315I cohorts, will therefore be defined as those in whom the T315I mutation is detected by direct sequencing.

It is possible that some patients with a history of T315I mutation will not demonstrate a detectable mutation at the time of trial entry. One potential explanation for this may be the well-described fall in the levels of T315I-containing CML clones, to below the limit of detection of the direct sequencing assay, when the selective pressure of TKI therapy is relaxed.[4] Such patients (T315I- but T315I history+) will fall into one of 2 groups: those treated with only imatinib, and those treated with dasatinib or nilotinib. Patients who have been treated with dasatinib or nilotinib will be enrolled and assigned to one of the resistant/intolerant cohorts, as they meet the protocol eligibility criteria for this group irrespective of the absence of the T315I mutation. Patients who have been treated with imatinib only, however, would only be eligible if they carry a detectable mutation. Nonetheless, these patients will be offered study treatment as their history of T315I mutation renders them unlikely to benefit from existing therapies. But, they will not be included in the T315I cohorts (A, C, or E) as they do not meet the study-specified definition of a T315I carrier. Based on our phase 1 experience, we project that a small number of patients will have a T315I history, but will not be negative for T315I by the direct sequencing assay result.

Since all patients who meet all eligibility criteria apart from the T315I determination will receive study drug, treatment initiation will be allowed once documentation is received by the central laboratory of receipt of the direct sequencing blood sample. Determination of inclusion in the T315I cohorts will be required prior to the first assessment of the primary endpoint, to avoid the introduction of bias in cohort assignment.

Statistical Analysis

Sample Size Determination, Cohorts A and B:

Data on the use of second generation TKIs in patients who have failed dasatinib and nilotinib are available in several small studies[5-7]. These 3 studies demonstrate an approximately 30% MCyR in these patients. However, these are highly selected patient populations; they do not include patients who have failed more than 2 agents, and responses are typically of short duration. Thus, for the purposes of this trial, the null or uninteresting MCyR rate is set at 20% for Cohort A (resistant and intolerant CP patients). The alternative MCyR rate is set at 35% for Cohort A. The overall alpha level for each cohort will be set at 0.05. With a cohort size of 100 patients, a minimum of 29 responders (ie, those with a CCyR and a PCyR) would need to be observed in Cohort A in order to observe an exact 95% CI such that the lower bound exceeds 20% and the upper bound exceeds 35%. Therefore, 100 patients will provide at least 85% power to distinguish between a null response rate of 20% and an alternative response rate of 35% in Cohort A. The study will also provide at least 98% power to distinguish between 20% and 40%, in which case 29 responses will also be required, and at least 78% power to distinguish between 30% and 45%, in which case 40 responses would be required.

With a cohort size of 100 patients, the maximum width of the exact 95% CI will be approximately 20% when the MCyR rate is in the expected range of 20% to 35%.

For Cohort B (T315I CP patients), the null or uninteresting MCyR rate is set at 10% and the alternative MCyR rate is set at 35%. Data on the use of second generation drugs [3,8] in these patients suggest that less than 10% of patients achieve MCyR.

With a cohort size of 60 patients, a minimum of 14 responders would need to be observed in Cohort B in order to observe an exact 95% CI such that the lower bound exceeds 10% and the upper bound exceeds 35%. Therefore, 60 patients will provide approximately 98% power to distinguish between a null response rate of 10% and an alternative response rate of 35% in Cohort B.

With a cohort size of 60 patients, the maximum width of the exact 95% CI will be 25% when the MCyR rate is in the expected range of 10% to 35%.

Sample Size Determination: Cohorts C-F

The sample sizes for Cohorts C to F (AP, and BP/Ph+ ALL) are based on similar considerations for each cohort. The endpoint for these cohorts is the MaHR. The MaHR rate is defined as the proportion of patients achieving a CHR or NEL response. The null or uninteresting MaHR rate is set at 10% and the alternative MaHR 30%. With a cohort size of 40 patients, a minimum of 9 responders would need to be observed in cohorts C to F in order to observe an exact 95% CI such that the lower bound exceeds 10% and the upper bound exceeds 30%. Forty patients in each cohort will provide approximately 89% power to distinguish between the null response rate of 10% and an alternative response rate of 30% in these cohorts.

Overall Sample Size:

For each disease phase, after the initiation of treatment, patients will be tested for the T315I mutation. Depending on the outcome of the test, patients will be assigned to a

resistant/intolerant cohort (cohorts A, C or E, respectively, depending on disease phase) or a T315I cohort (cohorts B, D, or F). For example, a CP patient will be tested and assigned to cohort A or B, an AP patient will be assigned to cohorts C or D, and a BP or Ph+ ALL patient will be assigned to cohort E or F. Therefore, enrollment and assignment to the paired cohorts comprising a disease phase are linked by the relative prevalence of T315I patients and the T315I testing scheme.

Early enrollment experience demonstrates that patients whose disease is resistant or intolerant to therapy are relatively more common than patients who carry the T315I mutation. Thus, the mutation testing schema will lead to a relative over-availability of resistant and intolerant patients compared with T315I patients. Therefore, cohorts A, C, and E may fill before the T315I cohorts B, D and F will reach their target sample sizes. Since the scientific objectives of the study require meeting the target accrual goals for the T315I cohorts (and, indeed, all cohorts), it is anticipated that the higher relative proportion of resistant/intolerant patients to T315I patients will require over-enrollment of the resistant/intolerant cohorts (A,C, and E) to ensure full T315I patient enrollment. Thus, overall enrollment will be determined by the need to fill the T315I cohorts.

Sample size considerations for each cohort

Cohort	Disease Phase	Eligibility Criterion	Primary Endpoint	Sample Size	Effect Size	Power
A	CP	R/I	MCyR	100	35% vs. 20% 40% vs. 20% 45% vs. 30%	≥85% ≥98% ≥78%
B	CP	T315I	MCyR	60	35% vs. 10% 25% vs. 10%	98% 85%
C	AP	R/I	MaHR	40	30% vs. 10%	90%
D	AP	T315I	MaHR	40	30% vs. 10%	90%
E	BP/Ph+ ALL	R/I	MaHR	40	30% vs. 10%	90%
F	BP/Ph+ ALL	T315I	MaHR	40	30% vs. 10%	90%

Analysis of Primary Endpoint

Cohorts A and B: The primary analysis of the primary endpoint of MCyR will be performed using a 2-sided exact 95% CI for the MCyR rate and will be based on the total patients enrolled in each cohort.

Cohorts C-F: The primary analysis of the primary endpoint of MaHR will be performed using a 2-sided exact 95% CI for MaHR rate and will be based on the total patients enrolled in each cohort.

Analysis of Secondary Endpoints:

Confirmed MCyR: The analysis of confirmed MCyR will be performed using a 2-sided exact 95% CI for the confirmed MCyR rate.

Duration of response: Duration of response will be estimated using the Kaplan-Meier method. The median duration of response and 95% CI will be calculated. An additional analysis will be performed defining the duration as the time from the first assessment at which the criteria for response are met until the last assessment at which the criteria for response are met.

- Loss of MCyR is defined as meeting any of the following criteria:
    - In patients entering the trial in PCyR: 2 consecutive cytogenetic assessments ≥ 28 days apart with Ph+ > 0%. Patients with a single cytogenetic assessment with Ph+ > 0% followed by no additional cytogenetic assessments will be also considered as meeting the criteria for loss of MCyR.
    - In patients entering the trial not in PCyR: 2 consecutive cytogenetic assessments 28 days apart with Ph+ > 35%. Patients with a single cytogenetic assessment with Ph+ > 35% followed by no additional cytogenetic assessments will be also considered as meeting the criteria for loss of MCyR.
- Loss of MaHR (Cohorts C through F) is defined as 2 consecutive hematologic assessments ≥ 4 weeks apart at which at the criteria for MaHR are not met. Patients with a single hematologic assessment at which the criteria for MaHR are not met followed by no additional hematologic assessments will be also considered as meeting the criteria for loss of MaHR.

Progression-free survival, overall survival, and time to response: Progression-free survival and overall survival, and time to response will be estimated using the Kaplan-Meier method. The median duration of response and 95% CI will be calculated.

- Patients who progress after a single missed or incomplete visit will be considered as having progressed at that visit.
- Patients who progress after 2 or more missed or incomplete visits will be censored at the last visit at which the response criteria are met.

Adverse Event (AE) Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related the medicinal product. Any worsening of a preexisting condition, which is temporally associated with the use of the study drug, is also an AE. The severity of AEs will be assessed according to the NCI CTCAE, v. 4.0

Adverse events include:

- Suspected adverse drug reactions;
- Reactions from study drug overdose, abuse, withdrawal, sensitivity, or toxicity;
- Significant changes or abnormalities when compared to baseline, in signs, symptoms, clinical laboratory results, or physiological testing. This includes any worsening of a preexisting condition temporally associated with the use of study drug;

- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, extensions of symptoms, or apparently unrelated illnesses.

Progression of disease is not considered an AE unless it results in hospitalization or death.

Determination of Adverse Event Seriousness

The Investigator will determine the seriousness of an AE based on the following criteria. AEs that do not fulfill the criteria below are classified as non-serious AEs.

Serious Adverse Event (SAE): An AE is considered an SAE if at least one of the following conditions applies:

- Death: An AE that results in death during the active study period or within 30 days following Study Drug administration.
- Life-threatening adverse event: An AE that places the patient, in the view of the Investigator, at immediate risk of death from the event as it occurred (ie, this does not include a reaction that had it occurred in a more severe form, might have caused death).
- Permanent, persistent, or significant disability: A disability is defined as any substantial disruption of a person's ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of existing hospitalization: Hospitalization refers to admission of a patient into a hospital for any length of time. Hospitalization for an elective or diagnostic procedure, or surgery for a pre-existing condition that has not worsened, is not considered an SAE.
- A congenital anomaly/birth defect: A fixed, permanent impairment established at or before birth.
- Cancer: Occurrence or diagnosis of a new cancer during the trial is considered a serious event.
- Overdose: Any AE associated with an overdose of study drug. An overdose of study drug is defined as an occurrence of administered dose exceeding that which is prescribed by the Investigator per protocol.
- Important medical event: Events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they jeopardize the patient and require medical or surgical intervention to prevent a life-threatening situation, hospitalization or death.

Dose Delays and Reductions

The table below describes guidelines for dose modification due to study-drug-related toxicity, graded according to NCI CTCAE 4.0. These guidelines should be followed by clinical investigators; however, for an individual patient, dose interruptions, reductions and treatment discontinuation should also be based on the clinical circumstance. Deviation from these guidelines should be communicated with the Sponsor. When the

observed toxicity has resolved to ≤ grade 1, the investigator may resume full dosing if clinically indicated.

There will be no dose modifications for grade 1 or 2 non-hematologic toxicities (except for pancreatitis and QTcF prolongation) attributable to the study drug that are manageable with supportive care or do not interfere with normal daily activities of the patient. In the event of a persistent grade 1 or 2 non-hematologic adverse drug reaction that is 1) intolerable due to clinical symptoms or interferes with normal daily activities, or 2) not controlled by optimal supportive care, the patient may be managed by dose delay or reduction as described in the table below. There are no suggested dose modifications for grade 1 or 2 hematologic toxicities.

Guidelines for assessment and management of pancreatitis and QTcF prolongation are described in the table below. Pancreatic toxicities may be manifest as an isolated elevation of pancreatic enzymes (amylase, lipase) in the absence of symptoms; or by enzyme elevation coupled with clinical symptoms. In the latter case, imaging should be performed, but in the case of isolated enzyme elevations it is optional. Refer to the table below for guidelines on management of pancreatitis with or without symptoms, and management of amylase/lipase elevations with or without symptoms.

In the event of a grade 3 or 4 AE attributed to study drug, the patient may be managed by dose reduction or delay as well. Guidelines are described in the table below. Note that grade 3 or 4 myelosuppression might be attributable to disease rather than study drug. In this case, if dose reduction or delay is deemed necessary, it is allowed.

Study drug administration may be delayed for up to 28 days to allow for improvement (to grade 1 or screening) or resolution of the event. If longer delays are necessary, the case should be discussed with the Medical Monitor of the study. In the event toxicity is intolerable and not controlled, a decision may be made by the Investigator to discontinue the patient from further study drug administration.

Modifications for AEs Attributable to Study Drug

Non-hematologic Toxicity	
Grade 2 Persistent 7 days with optimal care	• Hold ponatinib • Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg • Hold ponatinib • Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg • Hold ponatinib • Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg • Consider discontinuing ponatinib
Grade 3 or 4	• Hold ponatinib • Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg • Hold ponatinib • Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg • Consider discontinuing ponatinib
Pancreatitis	
Grade 2 (elevated amylase or lipase only)	See amylase/lipase section below
Grade 2 (mild symptoms or radiologic findings)	• Hold ponatinib • Perform ultrasound or abdominal CT scan with contrast • If imaging positive, continue holding ponatinib and repeat according to clinical care • If negative, or after resolution by imaging, resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg • Repeat above, except resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg • Repeat above, except resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg • Consider discontinuing ponatinib
Grade 3	• Hold ponatinib • Perform ultrasound or abdominal CT scan with contrast • If imaging is positive, continue holding ponatinib and repeat according to clinical care • If imaging is negative, or after resolution by imaging, resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg

	• Repeat above, except resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg • Repeat above • Consider discontinuing ponatinib
Grade 4	• Hold ponatinib • Consult Sponsor
Amylase/Lipase	
Grade ≤ 2	No intervention
Grade 3 or 4	• Hold ponatinib • Consider performing ultrasound or abdominal CT scan with contrast • If imaging positive, continue holding ponatinib and repeat according to clinical care • If negative, or after resolution by imaging, resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg • Repeat above • Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg • Repeat above • Consider discontinuing ponatinib
Prolonged QTcF	
Grade 2 (QTcF 481-500 ms)	• Hold ponatinib • Perform serum electrolyte analysis (including potassium, calcium and magnesium) and correct with supplements if below normal limits • Review concomitant medications • Repeat ECG as clinically indicated, but at least daily until QTcF returns to ≤ grade 1 (480 ms) • Resume at 45 mg after recovery to ≤ grade 1 • If no contributing reason was identified for QTcF elevation then weekly ECG monitoring is recommended for 4 weeks upon resumption of ponatinib, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated Recurrence at 45 mg • Repeat above • Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg • Repeat above • Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg • Discontinue ponatinib • Consult Sponsor

Grade 3 (QTcF ≥ 501 ms on at least 2 separate ECGs)	• Hold ponatinib • Perform serum electrolyte analysis (including potassium, calcium and magnesium) and correct with supplements if below normal limits • Review concomitant medications • Repeat ECG as clinically indicated, but at least daily until QTcF returns to ≤ grade 1 (480 ms) • Resume at 30 mg after recovery to ≤ grade 1 • If no contributing reason was identified for QTcF elevation then weekly ECG monitoring is recommended for 4 weeks upon resumption of ponatinib, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated Recurrence at 30 mg • Repeat above • Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg • Discontinue ponatinib • Consult Sponsor
Grade 4	• Discontinue ponatinib • Consult Sponsor
Hematologic	
ANC/platelets	
Grade 3 or 4	• Hold ponatinib • Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg • Hold ponatinib • Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg • Hold ponatinib • Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg • Consider discontinuing ponatinib

Appendix C: Response Criteria

The table below provides the response criteria used for assessment of the anti-leukemic activity of ponatinib.[1,9-12]

<table>
<tr><th>Disease</th><th colspan="2">Type of Response</th></tr>
<tr><td rowspan="2">CP-CML</td><td colspan="2">Complete Hematologic Response (CHR)</td></tr>
<tr><td colspan="2">▪ White blood count (WBC) ≤ institutional upper limit of normal (ULN)
▪ Platelets <450,000/mm³
▪ No blasts or promyelocytes in peripheral blood
▪ <5% myelocytes plus metamyelocytes in peripheral blood
▪ Basophils <5% in peripheral blood
▪ No extramedullary involvement (including no hepatomegaly or splenomegaly)</td></tr>
<tr><td rowspan="3">AP-CML, BP-CML and Ph+ ALL</td><td colspan="2">Major hematologic response (MaHR) defined as either:</td></tr>
<tr><td>Complete Hematologic Response (CHR)</td><td>No Evidence of Leukemia (NEL)</td></tr>
<tr><td>▪ White blood count (WBC) ≤ institutional upper limit of normal (ULN)
▪ Absolute neutrophil count (ANC) ≥1000/mm³
▪ Platelets ≥100,000/ mm³
▪ No blasts or promyelocytes in peripheral blood
▪ Bone marrow blasts ≤5%
▪ <5% myelocytes plus metamyelocytes in peripheral blood
▪ Basophils <5% in peripheral blood
▪ No extramedullary involvement (including no hepatomegaly or splenomegaly)</td><td>▪ WBC ≤ institutional ULN
▪ No blasts or promyelocytes in peripheral blood
▪ Bone marrow blasts ≤5%
▪ <5 % myelocytes plus metamyelocytes in peripheral blood
▪ Basophils <5% in peripheral blood
▪ No extramedullary involvement (including no hepatomegaly or splenomegaly)
▪ At least one of the following:
(i) 20,000/mm³ ≤ platelets < 100,000/mm³</td></tr>
</table>

		(ii) 500/mm³ ≤ ANC < 1000/mm³
CML (all phases) and Ph+ ALL	**Major Cytogenetic Response (MCyR)**	
	Defined as CCyR + PCyR	
	Complete Cytogenetic Response (CCyR)	
	Defined as no Ph+ cells in at least 20 metaphases	
	Partial Cytogenetic Response (PCyR)	
	Defined as 1% to 35% Ph+ cells	
CP-CML and AP-CML	**Major Molecular Response (MMR)**	
	Defined as ≤0.1% BCR-ABL transcripts on the International Scale (IS) (ie, ≤0.1% BCR-ABL^{IS}; IS reporting is restricted to the common e13(b2)a2/e14(b3)a2 BCR-ABL [p210] transcripts, in peripheral blood as measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR).	
	Molecular Response 4 (MR^{4})	
	Either detectable transcripts ≤0.01% BCR-ABL^{IS} or undetectable BCR-ABL transcripts in cDNA with ≥10,000 ABL transcripts, in peripheral blood as measured by RT-qPCR.	
	Molecular Response 4.5 (MR$^{4.5}$)	
	Either detectable transcripts ≤0.0032% BCR-ABL^{IS} or undetectable BCR-ABL transcripts in cDNA with ≥32,000 ABL transcripts, in peripheral blood as measured by RT-qPCR.	

Progression Criteria

Progression from CP[10]	• Death • Development of AP or BP • Loss of CHR (in the absence of cytogenetic response) confirmed by development in complete blood counts (CBC's) at least 4 weeks apart. • Loss of MCyR • Increasing WBC in patient without CHR, defined as doubling of WBC to >20,000/mm^3 on 2 occasions at least 4 weeks apart (after the first 4 weeks of therapy)
Progression from AP[13]	• Death • Development of confirmed BP • Loss of previous major or minor hematologic response over a 2-week period • No decrease from baseline levels in percentage blasts in peripheral blood or bone marrow on all assessments over a 4 week period
Progression from BP or Ph+ ALL[9]	• Death • Increasing blasts in peripheral blood or bone marrow over a 4 week period

Criteria for Progression from CP-CML to AP-CML or BP-CML

Patients who met the criteria for CP-CML at baseline and met at least one of the following criteria while on treatment:

- ≥15% blasts in peripheral blood or bone marrow
- ≥20% basophils in peripheral blood
- ≥30% blasts + promyelocytes in peripheral blood or bone barrow

Appendix D. End-of-Treatment BCR-ABL Mutational Analysis

Analysis

BCR-ABL mutational analysis was performed by bidirectional Sanger sequencing of real-time polymerase chain reaction (RT-PCR)-generated complementary deoxyribonucleic acid (cDNA) at a central laboratory (MolecularMD, Portland, Oregon, United States). This assay detects mutations between amino acids 30 to 510 of ABL. The limit of detection of the assay was approximately 10-20% (ie, direct sequencing was able to detect a mutation if at least 10-20% of the amplified BCR-ABL cDNA contained the mutation). When a mutation was detected, in both sequencing directions, an estimate of the percentage of cDNAs with the mutation was made (eg, 50% T315I indicated that the mutant and native nucleotides at that position were present in equal proportions). While this method does not allow direct detection of compound mutations, ie, the presence of two or more nucleotide mutations on a single BCR-ABL allele, the presence of a compound mutation was inferred by the detection of two (or more) mutations with a combined frequency >100% (eg, 100% T315I and 30% F317V).

BCR-ABL mutational analysis was performed on peripheral blood samples collected at baseline (BL) from all 444 cohort-assigned patients (439 had evaluable results) and on samples collected at end-of-treatment (EOT) from 123 of the 227 patients who discontinued treatment for any reason.

The mutation status of patients at EOT was compared to their status at BL. The analysis focused, in particular, on the mutation status of patients who achieved and then lost a response corresponding to the primary endpoint (MCyR for CP-CML patients and MaHR for AP-CML, BP-CML and Ph+ ALL patients), as defined in Appendix B. Of secondary interest were mutation(s) that were newly acquired at EOT, irrespective of response. Interpretation of the significance of mutations acquired at EOT took into account the degree to which the patient was exposed to ponatinib, represented as the average daily dose of ponatinib administered, and the reason for discontinuation as given by the investigator. Also considered were the patient's mutation history, prior TKI exposure, and time between last dose and collection of the EOT sample.

Results

CP-CML:

EOT mutation analysis was performed on 56 of 99 patients who discontinued.

Six patients lost MCyR and discontinued ponatinib for any reason. Of these, 4 patients had EOT mutations assessed. As shown in Table A, at EOT, the mutation status of all 4 patients who lost MCyR was unchanged from BL.

Of the remaining 52 patients, 5 patients lost a mutation at EOT that was present at BL, 42 patients had no change in mutation status, and 5 patients gained a mutation (Table B). The characteristics of these 5 patients were as follows:

- In a patient that had a low average daily dose of ponatinib (12 mg), an E255V mutation was detected at low percentage (10%) at EOT that was not detected at BL. This mutation had previously been detected in this patient. This patient did not achieve a response to ponatinib and discontinued due to physician decision. Responses in other patients with E255V have been observed (Table S6).
- In a second patient, an F359V mutation that was detected at BL was lost and a T315I mutation, which had been detected historically, was gained. This patient did not achieve a response to ponatinib and discontinued due to progressive disease. Responses in other patients with T315I have been observed (Table S6).
- The remaining 3 patients had evidence of acquisition of compound mutations.
    - One patient did not achieve a response on ponatinib, discontinued (reason given as Other – stem cell transplant), and had a T315I/M351T compound mutation at EOT. This patient had T315I at baseline.
    - A second patient achieved a CCyR, discontinued due to an adverse event (myelodysplastic syndrome) without documented loss of response and had a T315I/F359V compound mutation at EOT. This patient had a history of T315I. The average daily dose in this patient was 30 mg/day.
    - A third patient achieved a CCyR, discontinued due to progressive disease (reason given by investigator) without documented loss of response, and had a Y253H/F359V compound mutation at EOT. This patient had a history of both mutations, and F359V was present at baseline. The average dose intensity in this patient was 26 mg/day.

In summary, no single mutation that confers resistance to ponatinib in CP-CML has been observed to date. No evaluable patient who lost MCyR acquired a single new mutation at EOT. The only single mutations newly detected at EOT (E255V and T315I) were A) not associated with loss of response in those patients and B) were associated with responses in other patients presenting with these mutations at BL (Table S6).

Compound mutations were detected in 3 patients at EOT. All three patients had one of the involved mutations at baseline and/or a history of one of the involved mutations. In one patient the compound mutation (Y253H/F359V) may have been associated with progressive disease.

AP-CML:

EOT mutation analysis was performed on 25 of 40 patients who discontinued.

Fourteen patients lost MaHR and subsequently discontinued for any reason. Of these, 10 patients had EOT mutations assessed. As shown in Table C, the EOT mutation status of 6 of these patients was unchanged from BL, and 4 patients gained a mutation. The 4 patients who gained a mutation are described as follows.

- In one patient, a T315I mutation was gained and in a second, an E255K mutation was gained. Both patients had a relatively low average daily dose of ponatinib (14-15 mg). Responses have been observed in other patients with these mutations (Table S6).
- In one patient, the compound mutation E255K/T315I was gained. This patient had T315I at baseline and had a relatively high dose intensity of ponatinib (38 mg/day).
- In one patient, E255M was gained. E255M is considered a compound mutation since 2 nucleotide changes are required to effect the E to M amino acid change; however, the appearance of E255M could also be the result of a combination of the single nucleotide mutations E255K and E255V, which would be indistinguishable from E255M by Sanger sequencing. This patient had a relatively high dose intensity of ponatinib (37 mg/day). Responses in other patients with E255K and E255V have been observed (Table S6).

Of the remaining 15 patients, 14 patients had no change in mutation status and 1 patient underwent EOT mutation testing 245 days after the last dose of ponatinib, which showed the gain of a compound mutation, with one of the involved mutations being present at baseline. This patient discontinued due to an AE and did not achieve MaHR on study. The mutation status of this patient at the time of ponatinib discontinuation is not known (Table D).

In summary, no single mutation that confers resistance to ponatinib in AP-CML has been observed to date. Though T315I and E255K single mutations emerged at EOT in patients who lost MaHR, responses have been observed in other patients presenting with these mutations at BL (Table S6). A compound mutation (E255K/T315I) emerged at EOT in one patient with T315I at baseline who lost MaHR.

BP-CML and Ph+ ALL

EOT mutation analysis was performed on 42 of 88 patients who discontinued.

Twenty-three patients lost MaHR and 22 subsequently discontinued for any reason. Of these, 10 patients had EOT mutations assessed. The EOT mutation status of 4 of these patients was unchanged from BL, and 6 patients gained a mutation (Tables E and G).

- All 6 patients had 1 mutation at BL and 2 (or 3) mutations at EOT.
    - In 4 patients, these are likely to be compound mutations (Y253H/E255K, E255V/F317I [n=2], E255K/T315I), and all patients had one of the involved mutations at baseline.
    - In the other 2 patients, it was not possible to determine whether the mutations are compound or multiple mutations due to the limitations of Sanger sequencing (T315I/F359C, E279K/T315I/A380S). Both patients had one of the associated mutations present at baseline. Responses in patients with T315I and F359C have been observed (Table S6), and responses in patients with E279K were observed in one patient with CP-

CML (data on file) in this trial and in one AP-CML patient in the phase 1 trial.[14] A380S was present at the lower level of detection of the assay (10%).

Of the remaining 32 patients, 1 patient had a history of T315I, did not have a BL mutation assessment, and had T315I at EOT, 2 patients lost a mutation at EOT that was present at BL, 12 patients had no change in mutation status, and 17 patients gained a mutation (Tables F and H).

- In 2 patients, a single mutation was gained at EOT. In 1 patient, T315I was seen at EOT, and in 1 patient T315I was lost and Y253H was observed at low level (10%).
- In the remaining patients, the gain resulted in the presence of 2 (n=8), 3 (n=6), or 5 (n=1) mutations at EOT, most of which involved compound mutations.

In summary, compound mutations that emerged at EOT were associated with resistance to ponatinib in BP-CML and Ph+ ALL patients. In all cases, compound mutations emerged in patients entering the study with one of the mutations at baseline.

Table A: CP-CML patients who lost MCyR and discontinued

Prior TKI Exposure[a]	Mutation History	Mutation Status on Cycle 1 Day 1	BCR-ABL Estimated % Mutation at Cycle 1 Day 1	Mutation Status at End of Treatment	BCR-ABL Estimated % Mutation at End of Treatment	Days Between Last Dose and EOT Mutation Analysis	Average Daily Dose (mg)	Duration of MCyR (months)	Reason for Discontinuation
Imat, Dasat, Nilot		None		None		5	37	2.8	PD
Imat, Dasat, Nilot, Bosut	G250E	G250E	100%	G250E	100%	21	15	5.5	AE
Imat, Dasat, Nilot	None	None		None		2	45	5.3	PD
Imat, Dasat, Nilot	F311L/F317L	F311L	90%	F311L	90%	28	29	2.8	AE
Imat, Dasat	None	None		ND			23	2.7	AE
Imat, Dasat, Nilot, Bosut	E255V	E255V	100%	ND			28	3.1	Lack of efficacy

PD=progressive disease; AE= adverse event; ND=not done

[a]TKIs = imatinib (imat), dasatinib (dasat), nilotinib (nilot), bosutinib (bosut)

Table B: CP-CML patients with gain of mutation at EOT

Prior TKI Exposure[a]	Mutation History	Mutation Status on Cycle 1 Day 1	BCR-ABL Estimated % Mutation on Cycle 1 Day 1	Mutation Status at End of Treatment	BCR-ABL Estimated % Mutation at End of Treatment	Days Between Last Dose and EOT Mutation Analysis	Average Daily Dose (mg)	Duration of MCyR (months)	Reason for Discontinuation
Imat, Dasat	E255V, T315I	None		E255V	10%	86	12		Physician decision
Imat, Dasat, Nilot	F359V, T315I	F359V	90%	T315I	100%	7	35		PD
Bosut	T315I	T315I	50%	T315I, M351T	100%, 40%	2	45		Other: stem cell transplant
Imat, Dasat	T315I	None		T315I, F359V	100%, 90%	9	30	<1[b]	AE
Imat, Dasat, Nilot	D267G, D276G, E499E, F359V, V299L, Y253H	V299L, F359V	100%, 100%	Y253H, F359V	100%, 100%	38	26	<1[b]	PD

PD=progressive disease; AE= adverse event

[a]TKIs = imatinib (imat), dasatinib (dasat), nilotinib (nilot), bosutinib (bosut)

[b]Discontinued prior to loss of MCyR

Table C: AP-CML Patients who lost MaHR and discontinued

Prior TKI Exposure[a]	Mutation History	Mutation Status on Cycle 1 Day 1	BCR-ABL Estimated % Mutation Cycle 1 Day 1	Mutation Status at End of Treatment	BCR-ABL Estimated % Mutation at End of Treatment	Days Between Last Dose and EOT Mutation Analysis	Average Daily Dose (mg)	Duration of MaHR (months)	Reason for Discontinuation
Imat, Dasat, Nilot	None	None		None		87	15	6.9	Other: no response
Imat, Dasat	T315I	None		None		37	29	3.0	PD
Imat, Dasat, Nilot	T315I	T315I	100%	T315I	100%	2	36	1.6	PD
Imat, Dasat	T315I	T315I	90%	T315I	100%	2	45	1.7	PD
Imat, Nilot	T315I	None		None		5	19	11.8	Other: stem cell transplant
Imat, Dasat	None	None		None		16	27	5.2	AE
Imat, Dasat	None	F317L	70%	T315I	40%	4	14	17.7	PD
Imat, Dasat, Nilot	None	None		E255K	100%	2	15	1.4	PD
Imat	T315I	T315I, H396V	90%, 10%	E255K, T315I	100%, 100%	5	38	1.4	PD
Imat, Nilot	None	None		E255M[b]	50%	17	37	4.1	PD
Imat, Dasat	None	None		ND			15	6.8	PD
Imat, Nilot	None	None		ND			45	3.0	Death
Imat, Nilot	T315I	None		ND			18	8.9	Other: stem cell transplant
Imat, Dasat, Nilot	M244V, T315I	T315I	100%	ND			36	5.7	PD

PD=progressive disease; AE= adverse event; ND=not done

[a]TKIs = imatinib (imat), dasatinib (dasat), nilotinib (nilot), bosutinib (bosut)

[b]E255M is considered a compound mutation since 2 nucleotide changes are required to effect the E to M amino acid change; however, the appearance of E255M could also be the result of a combination of the single nucleotide mutations E255K and E255V, which would be indistinguishable from E255M by Sanger sequencing.

Table D: AP-CML patients who gained mutations at EOT (excludes patients captured in Table C):

Prior TKI Exposure[a]	Mutation History	Mutation Status on Cycle 1 Day 1	BCR-ABL Estimated % Mutation Cycle 1 Day 1	Mutation Status at End of Treatment	BCR-ABL Estimated % Mutation at End of Treatment	Days Between Last Dose and EOT Mutation Analysis	Average Daily Dose	Duration of MaHR (months)	Reason for Discontinuation
Imat, Dasat	E275K, E275Q, G250E, M351T	G250E, M351T	10%, 90%	G250E, E275K, F317L	70%, 100%, 10%	245	45		AE

PD=progressive disease; AE= adverse event
[a]TKIs = imatinib (imat), dasatinib (dasat), nilotinib (nilot), bosutinib (bosut)

Table E: BP-CML patients who lost MaHR and discontinued

Prior TKI Exposure[a]	Mutation History	Mutation Status on Cycle 1 Day 1	BCR-ABL Estimated % Mutation at Cycle 1 Day 1	Mutation Status at End of Treatment	BCR-ABL Estimated % Mutation at End of Treatment	Days Between Last Dose and EOT Mutation Analysis	Average Daily Dose (mg)	Duration of MaHR (months)	Reason for Discontinuation
Imat, Dasat, Nilot	None	None		None		2	44	6.0	Other: stem cell transplant
Imat, Dasat	T315I	T315I	60%	T315I	100%	1	42	4.1	PD
Imat, Dasat, Nilot	T315I	T315I	50%	T315I	80%	2	41	1.8	PD
Imat, Dasat, Nilot	Y253H	Y253H	100%	Y253H, E255K	100%, 30%	4	43	3.2	PD
Imat, Nilot		F359C	50%	T315I, F359C	50%, 50%	15	45	2.0	PD
Imat, Dasat, Nilot	E459K, F317L, F359V	F317L, F359V	100%, 100%	ND			37	2.8	Death
Imat, Dasat, Nilot	None	None		ND			42	1.8	AE
Imat, Dasat, Nilot	T315I	T315I	50%	ND			36	2.7	PD
Imat, Dasat	T315I	T315I	80%	ND			30	3.5	AE
Imat, Dasat	T315I	T315I	40%	ND			45	4.7	PD

PD=progressive disease; AE= adverse event; ND=not done

[a]TKIs = imatinib (imat), dasatinib (dasat), nilotinib (nilot), bosutinib (bosut)

Table F: BP-CML patients with gain of mutation at EOT (excludes patients in Table E)

Prior TKI Exposure[a]	Mutation History	Mutation Status on Cycle 1 Day 1	BCR-ABL Estimated % Mutation on Cycle 1 Day 1	Mutation Status at End of Treatment	BCR-ABL Estimated % Mutation at End of Treatment	Days Between Last Dose and EOT Mutation Analysis	Average Daily Dose (mg)	Duration of MaHR (months)	Reason for Discontinuation
Imat, Dasat	T315I	None		T315I	40%	2	45		PD
Imat, Dasat, Nilot		F317L, F359V	60%	E255K, F359V	30%, 100%	6	44		PD
Imat, Dasat, Bosut	T315I	T315I	100%	E255M, T315I	50%, 100%	2	45		PD
Imat, Dasat	None	None		E255V, T315I	40%, 60%	4	45		PD
Imat, Dasat	T315I	T315I	60%	E255K, T315I	50%, 50%	39	34		AE
Imat, Dasat, Nilot	None	T315I	50%	Q252H, T315I	10%, 50%	1	44		PD
Imat	T315I	T315I	100%	T315I, F359V	100%, 100%	7	24		PD
Imat, Dasat, Nilot	G250E, V299L	G250E, V299L	100%, 100%	G250E, E255K,V299L	100%, 100%, 100%	23	35		PD
Imat, Dasat	E255K, Q252H, T315I	E255K	100%	Q252H, E255K, T315I	90%, 100%, 10%	2	45		PD
Dasat	T315I/ Y235F	T315I	100%	Q252H, E255K, T315I	80%, 20%, 100%	1	45		PD
Imat, Dasat, Nilot	E255K, E255M, E255V, G250E, T315A, T315I	G250E, T315A	100%, 100%	G250E, E255V, T315A	100%, 100%, 100%	2	43		PD
Imat, Dasat, Nilot	F359C	F359C	100%	Y253H, E255K, L298V, T315I, F359C	10%, 40%, 20%, 40%, 100%	6	38		AE

PD=progressive disease; AE= adverse event; ND=not done

[a]TKIs = imatinib (imat), dasatinib (dasat), nilotinib (nilot), bosutinib (bosut)

Table G: Ph+ ALL patients who lost MaHR and discontinued

Prior TKI Exposure[a]	Mutation History	Mutation Status on Cycle 1 Day 1	BCR-ABL Estimated % Mutation on Cycle 1 Day 1	Mutation Status at End of Treatment	BCR-ABL Estimated % Mutation at End of Treatment	Days Between Last Dose and EOT Mutation Analysis	Average Daily Dose (mg)	Duration of MaHR (months)	Reason for Discontinuation
Dasat	T315I	T315I	100%	T315I	100%	2	45	2.3	PD
Imat, Dasat		F317I	100%	E255V, F317I	100%, 100%	1	45	3.2	PD
Dasat	F317I	F317I	100%	E255V, F317I	100%, 100%	2	20	6.4	AE
Imat, Dasat, Nilot	T315I	T315I	100%	E255K, T315I	30%, 100%	2	45	4.3	Lack of efficacy
Imat, Dasat	None	T315I	60%	E279K[b], T315I, A380S	40%, 50%, 10%	2	40	1.8	PD
Imat, Dasat, Nilot	None	ND		ND			45	2.7	PD
Dasat	T315I	T315I	100%	ND			44	3.2	PD
Imat, Dasat, Nilot	T315I	T315I	80%	ND			42	3.4	PD
Imat, Dasat	T315I	None		ND			18	7.4	Death
Imat, Dasat, Nilot	F317L, G250E	G250E, F317L	50%, 100%	ND			45	1.8	PD
Imat, Dasat	Y253H	T315I	100%	ND			41	2.2	PD
Imat, Dasat, Nilot	E255K, T315I	T315I	90%	ND			44	4.7	AE

PD=progressive disease; AE= adverse event; ND=not done
[a]TKIs = imatinib (imat), dasatinib (dasat), nilotinib (nilot), bosutinib (bosut)
[b]One patient (CP-CML) in this study had E279K at baseline and had a response (MMR). One patient (AP-CML) in the phase 1 study had E279K at baseline and had a response (MaHR, PCyR).[14]

Table H: Ph+ ALL patients with gain of mutation at EOT (excludes patients captured in Table G)

Prior TKI Exposure[a]	Mutation History	Mutation Status on Cycle 1 Day 1	BCR-ABL Estimated % Mutation on Cycle 1 Day 1	Mutation Status at End of Treatment	BCR-ABL Estimated % Mutation at End of Treatment	Days Between Last Dose and EOT Mutation Analysis	Average Daily Dose (mg)	Duration of MaHR (months)	Reason for Discontinuation
Imat, Dasat, Nilot	T315I	T315I	50%	Y253H	10%	2	45	0	PD
Imat	T315I	T315I	100%	E255K, T315M	10%, 90%	2	45	0	PD
Imat, Dasat	T315I	T315I	100%	E255K, T315I	50%, 100%	2	45	0	PD
Imat, Dasat	T315I	T315I	100%	T315I, M351T, F359V	100%, 10%, 10%	5	45	0	Lack of efficacy
Imat, Dasat	F359V, T315I	T315I	100%	E255K, T315I, T315M	90%, 100%, 10%	2	52	0	PD

PD=progressive disease; AE= adverse event
[a]TKIs = imatinib (imat), dasatinib (dasat), nilotinib (nilot), bosutinib (bosut)

Figure S1: Process for Assigning Resistant/Intolerant and T315I Cohorts

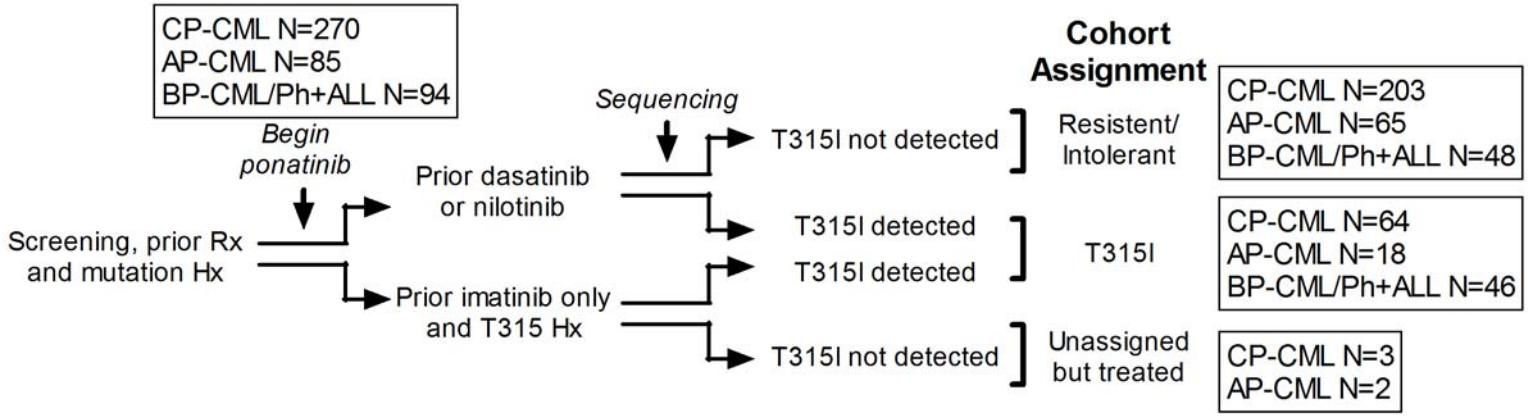

Table S1. Demographic and Baseline Characteristics (Expanded)

Characteristic	CP-CML N=270	AP-CML N=85	BP-CML N=62	Ph+ ALL N=32	Total N=449
Age					
Median (range), years	60 (18-94)	60 (23-82)	53 (18-74)	62 (20, 80)	59 (18-94)
≥65 years, n (%)	101 (37)	27 (32)	14 (23)	13 (41)	155 (35)
ECOG performance status, n (%)					
0	189 (70)	47 (55)	20 (32)	11 (34)	267 (60)
1	77 (29)	31 (37)	22 (35)	17 (53)	147 (33)
2	4 (1)	7 (8)	19 (31)	4 (13)	34 (8)
Median time (range) from diagnosis, years	7.0 (0.5-27.4)	7.0 (0.3-28.5)	4.0 (0.5-27.2)	1.5 (0.5-7.8)	6.1 (0.3-28.5)
Prior tyrosine kinase inhibitor therapy[a], n (%)					
≥2 tyrosine kinase inhibitors	252 (93)	80 (94)	59 (95)	26 (81)	417 (93)
≥3 tyrosine kinase inhibitors	161 (60)	51 (60)	37 (60)	13 (41)	262 (58)
Prior approved tyrosine kinase inhibitors, n (%)					
Imatinib	261 (97)	84 (99)	58 (94)	27 (84)	430 (96)
Dasatinib	217 (80)	70 (82)	58 (94)	30 (94)	375 (84)
Nilotinib	184 (68)	56 (66)	41 (66)	13 (41)	294 (65)
Bosutinib	24 (9)	5 (6)	4 (6)	0	33 (7)
Number of prior approved tyrosine kinase inhibitors, n (%)					
1	19 (7)	5 (6)	3 (5)	6 (19)	33 (7)
2	98 (36)	33 (39)	22 (35)	14 (44)	167 (37)
3	141 (52)	44 (52)	34 (55)	12 (38)	231 (51)
4	12 (4)	3 (4)	3 (5)	0	18 (4)
Median time (range) on prior tyrosine kinase inhibitors[a], years	5.4 (0.4 – 13.3)	5.1 (0.3 – 12.1)	2.0 (0.1 – 11.6)	1.2 (0.1 – 8.2)	4.6 (0.1 – 13.3)

Characteristic	CP-CML N=270	AP-CML N=85	BP-CML N=62	Ph+ ALL N=32	Total N=449
Other prior therapy, n (%)					
Cytarabine	46 (17)	21 (25)	22 (35)	14 (44)	103 (23)
Interferon[b]	103 (38)	37 (44)	11 (18)	0 (0)	151 (34)
Stem cell transplant	12 (4)	8 (9)	11 (18)	9 (28)	40 (9)
Resistance/intolerance to dasatinib or nilotinib at any time, n (%)[c, d]					
Resistant[e]	214 (84)	74 (93)	59 (97)	27 (90)	374 (88)
Intolerant only[f]	40 (16)	6 (8)	2 (3)	2 (7)	50 (12)
Not specified	2 (1)	0	0	1 (3)	3 (1)
Resistance/intolerance to dasatinib at any time, n (%)[c,g]					
Resistant	149 (69)	56 (80)	44 (76)	23 (77)	272 (73)
Intolerant only	65 (30)	12 (17)	13 (22)	5 (17)	95 (25)
Not specified	3 (1)	2 (3)	1 (2)	2 (7)	8 (2)
Resistance/intolerance to nilotinib at any time, n (%)[c,g]					
Resistant	132 (72)	45 (80)	30 (73)	8 (62)	215 (73)
Intolerant only	41 (22)	6 (11)	2 (5)	2 (15)	51 (17)
Not specified	11 (6)	5 (9)	9 (22)	3 (23)	28 (10)
Cytogenetic status at enrollment, n (%)					
CCyR[h]	0	1 (1)	3 (5)	2 (6)	6 (1)
PCyR[i]	53 (20)	1 (1)	3 (5)	8 (25)	65 (14)
Less than PCyR	215 (80)	80 (94)	51 (82)	20 (63)	366 (82)
Missing or less than 20 metaphases examined	2 (1)	3 (4)	5 (8)	2 (6)	12 (3)

Characteristic	CP-CML N=270	AP-CML N=85	BP-CML N=62	Ph+ ALL N=32	Total N=449
Hematologic status at enrollment, n (%)					
MaHR	N/A	14 (16)[j]	0	0	
CHR	113 (42)	N/A	N/A	N/A	
Bone marrow blasts not determined	N/A	1 (1)[k]	4 (6)	0	
Best response to most recent dasatinib or nilotinib containing regimen, n/N (%)[d]					
MaHR or better[l]	N/A	17 (21)	9 (15)	13 (43)	
MCyR or better[m]	66 (26)	12 (15)	7 (11)	8 (27)	
MMR	8 (3)	2 (3)	1 (2)	5 (17)	

N/A=not applicable

[a]Includes approved and investigational tyrosine kinase inhibitors; Prior investigational tyrosine kinase inhibitors (≥1%): radotinib (2%), bafetinib (2%), DCC-2036 (2%), XL228 (2%),

[b]Includes interferon, interferon-α2a, interferon α-2b, pegylated interferon

[c]Intolerant patients were required to have active disease (eg, could not be in CCyR [CP- CML] or MaHR [AP-CML, BP-CML, Ph+ ALL]);

[d]Percentages are calculated based on the number of patients who received prior dasatinib or nilotinib; CP- CML N=256, AP-CML N=80, BP-CML N=61, Ph+ ALL N=30

[e]Patients demonstrating resistance to one tyrosine kinase inhibitor and intolerance to the other were counted as resistant

[f]Patients may have been resistant and/or intolerant to tyrosine kinase inhibitors other than nilotinib or dasatinib

[g]Percentanges are calculated based on the number of patients who received prior dasatinib or nilotinib

[h]Patients entering the trial in CCyR were considered non-responders for cytogenetic response.

[i]Patients entering the trial in PCyR had to achieve CCyR to be considered as achieving MCyR

[j]These patients were enrolled and treated despite not meeting the eligibility criteria. These patients were counted as non-responders in the analysis of MaHR

[k]This patient was counted as a non-responder in the analysis of MaHR

[l]MaHR + PCyR + CCyR + MMR

Characteristic	CP-CML N=270	AP-CML N=85	BP-CML N=62	Ph+ ALL N=32	Total N=449
[m]PCyR+ CCyR + MMR					

Table S2: Mutation Status at Baseline

	CP-CML		AP-CML		BP-CML		Ph+ ALL	
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=38	T315I N=24	R/I N=10	T315I N=22
BCR-ABL mutation status, n (%)								
Patients with no sequencing data	0	0	2 (3)	0	2 (5)	0	1 (10)	0
Patients with no mutations	136 (67)	0	39 (60)	0	17 (45)	0	3 (30)	0
Patients with 1 mutation	55 (27)	50 (78)	20 (31)	16 (89)	12 (32)	21 (88)	4 (40)	15 (68)
Patients with ≥2 mutations	12 (6)	14 (22)	4 (6)	2 (11)	7 (18)	3 (13)	2 (20)	7 (32)
Baseline mutations in >1 patient overall, n (%)								
T315I	0	64 (100)	0	18 (100)	0	24 (100)	0	22 (100)
F317L	19 (9)	3 (5)	8 (12)	0	4 (11)	0	1 (10)	1 (5)
E255K	5 (3)	3 (5)	3 (5)	0	5 (13)	1 (4)	1 (10)	0
F359V	12 (6)	1 (2)	1 (2)	0	2 (5)	1 (4)	0	0
G250E	7 (3)	1 (2)	2 (3)	0	3 (8)	0	1 (10)	0
Y253H	2 (1)	0	2 (3)	0	2 (5)	1 (4)	1 (10)	2 (9)
V299L	4 (2)	1 (2)	1 (2)	0	3 (8)	0	0	0
E255V	2 (1)	0	2 (3)	0	2 (5)	0	0	2 (9)
M244V	4 (2)	1 (2)	1 (2)	1 (6)	1 (3)	0	0	0
F359C	2 (1)	2 (3)	0	0	2 (5)	0	0	0
H396R	4 (2)	1 (2)	1 (2)	0	0	0	0	0
F359I	3 (1)	1 (2)	0	0	0	0	0	0
E355A	1 (<1)	1 (2)	1 (2)	0	0	0	0	0
E459K	3 (1)	0	0	0	0	0	0	0
F311L	1 (<1)	0	1 (2)	0	0	0	0	1 (5)
L248V	1 (<1)	1 (2)	1 (2)	0	0	0	0	0

	CP-CML		AP-CML		BP-CML		Ph+ ALL	
	R/I N=203	**T315I N=64**	**R/I N=65**	**T315I N=18**	**R/I N=38**	**T315I N=24**	**R/I N=10**	**T315I N=22**
E450G	1 (<1)	0	1 (2)	0	0	0	0	0
F317I	0	0	0	0	0	0	2 (20)	0
L298V	1 (<1)	0	1 (2)	0	0	0	0	0
M351T	0	1 (2)	1 (2)	0	0	0	0	0

Table S3: Hematologic, Cytogenetic, and Molecular Responses by Cohort

	CP-CML		AP-CML		BP-CML/Ph+ ALL	
	R/I N=203	**T315I N=64**	**R/I N=65**	**T315I N=18**	**R/I N=48**	**T315I N=46**
CHR, n (%)[a]	192 (95)	58 (91)	N/A	N/A	N/A	N/A
MaHR, n (%)[b]	N/A	N/A	37 (57)	9 (50)	17 (35)[c]	15 (33)[d]
Any CyR[e]	128 (63)	52 (81)	34 (52)	12 (67)	19 (40)	20 (43)
MCyR, n (%)	104 (51)[f]	45 (70)[f]	22 (34)	10 (56)	13 (27)	16 (35)
CCyR, n (%)	82 (40)	42 (66)	14 (22)	6 (33)	11 (23)	12 (26)
PCyR, n (%)	22 (11)	3 (5)	8 (12)	4 (22)	2 (4)	4 (9)
MMR, n (%)[g]	55 (27)	36 (56)	9 (14)	4 (22)	N/A	N/A
MR^4, n (%)	34 (17)	22 (34)	4 (6)	0	N/A	N/A
$MR^{4.5}$, n (%)	24 (12)	15 (23)	4 (6)	0	N/A	N/A
Median time (range) to MCyR (CP) or MaHR (AP, BP, Ph+ ALL) for responders, months	2.8 (1.8-11.3)	2.8 (1.6-10.9)	0.7 (0.4-3.7)	0.6 (0.5-5.8)	0.9 (0.5-5.5)	0.8 (0.4-1.9)

CHR=complete hematologic response; N/A=not applicable; MaHR=major hematologic response; MCyR (CCyR + PCyR)=major cytogenetic response; CCyR=complete cytogenetic response; PCyR=partial cytogenetic response; MMR =major molecular response = MR^3 only + MR^4 only +$MR^{4.5}$.

[a]The CHR rate includes patients maintaining or achieving CHR on study. CP-CML patients with CHR at baseline: R/I N=89, T315I N=24.

[b]Patients missing baseline bone marrow blasts and those entering the study in MaHR are counted as non-responders in the analysis of MaHR; 14 AP-CML patients entered the study in MaHR, and 1 AP-CML patient had missing baseline bone marrow blasts.

[c]The MaHR rate for R/I BP-CML patients was 12/38 (32%); the MaHR rate for R/I Ph+ ALL patients was 5/10 (50%).

[d]The MaHR rate for T315I BP-CML patients was 7/24 (29%); the MaHR rate for T315I Ph+ ALL patients was 8/22 (36%).

[e]Any CyR=CCyR + PCyR + minor CyR + minimal CyR

[f]CP-CML patients who entered the study in PCyR had to achieve CCyR to meet the criteria for MCyR. In the R/I and T315I cohorts, 39 and 13 patients entered the study in PCyR, respectively. The MCyR rates for these patients were 64% and 92% for R/I and T315I, respectively, and 71% overall.

[g]Molecular responses were measured in peripheral blood.

Table S4: Prespecified Subgroup Analyses in CP-CML (N=267)

	MCyR n (%)
Age	
18-44 years (n=54)	39 (72)
45-64 years (n=113)	70 (62)
≥65 years (n=100)	40 (40)
Time since diagnosis	
<3.29 years (n=73)	44 (60)
3.29-9.09 years (n=95)	62 (65)
>9.09 years (n=99)	43 (43)
P-values for Age comparisons: 18-44 years vs. 45-64 years, P=0.2258 18-44 years vs. ≥65 years, P<0.001 45-64 years vs. ≥65 years, P=0.0016 P-values for Time Since Diagnosis comparisons: <3.29 years vs. 3.29-9.09 years, P=0.5229 <3.29 years vs. >9.09 years, P=0.0319 3.29 years-9.09 years vs. >9.09 years, P=0.0026	

Table S5. Selected Characteristics by Cohort

Characteristic	CP-CML[a]		AP-CML[a]		BP-CML		Ph+ ALL	
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=38	T315I N=24	R/I N=10	T315I N=22
Median follow-up, months (range)	16 (0.1-25)	15 (1-22)	16 (4-25)	14 (4-25)	6 (0.1-21)	6 (0.4-18)	12 (1-19)	5 (0.1-16)
Median age at baseline, years (range)	61 (22-94)	52 (18-87)	60 (23-82)	54 (24-78)	55 (18-74)	45 (18-74)	54 (20-74)	63 (23-80)
Median time since diagnosis at baseline, years (range)	7.8 (0.5-27.4)	4.8 (1.2-19.5)	7.1 (0.3-28.5)	6.6 (1.2-15.9)	5.1 (0.6-27.2)	2.1 (0.5-14.1)	1.9 (1.0-7.8)	1.4 (0.5-6.6)
Prior tyrosine kinase inhibitors[b]								
Median number, n (%)	3.0	2.0	3.0	2.5	3.0	2.0	3.0	2.0
2, n (%)	64 (32)	27 (42)	22 (34)	6 (33)	10 (26)	12 (50)	3 (30)	10 (45)
≥3, n (%)	135 (67)	26 (41)	42 (65)	9 (50)	27 (71)	10 (42)	6 (60)	7 (32)
Best response to most recent dasatinib or nilotinib containing regimen, n/N (%)[c]								
MaHR or better[d]	N/A	N/A	14 (22)	3 (20)	6 (16)	3 (13)	6 (60)	7 (35)
MCyR or better[e]	53 (26)	13 (25)	9 (14)	3 (20)	4 (11)	3 (13)	3 (30)	5 (25)
MMR or better	7 (3)	1 (2)	1 (2)	1 (7)	0	1 (4)	2 (20)	3 (15)
Median dose intensity, mg/day (range)	30 (3-45)	39 (13-45)	31 (5-45)	41 (8-45)	42 (15-47)	44 (20-47)	45 (18-45)	45 (27-52)

[a]Five patients (3 CP-CML, 2 AP-CML) were post-imatinib but non-T315I at baseline; these patients were treated but not assigned to a cohort and are not represented here

[b]Includes both approved and investigational tyrosine kinase inhibitors

[c]Percentages are calculated based on the number of patients who received prior dasatinib or nilotinib; CP- CML R/I N=203, T135I N=53; AP- CML R/I N=65, T315I N=15; BP-CML R/I N=38, T315I N=23; Ph+ ALL R/I N=10, T315I N=20

[d]MaHR + PCyR + CCyR + MMR

[e]PCyR+ CCyR + MMR

Table S6: Response by Baseline Mutation Status

	No mutation detected[a]	Mutations other than T315I	T315I only	Mutations in addition to T315I	1 mutation	2 mutations	3+ mutations
CP-CML	**N=136**	**N=67**	**N=50**	**N=14**	**N=105**	**N=22**	**N=4**
CHR, n (%)	132 (97)	60 (90)	47 (94)	11 (79)	96 (91)	19 (86)	3 (75)
MCyR, n (%)	66 (49)	38 (57)	37 (74)	8 (57)	67 (64)	15 (68)	1 (25)
CCyR, n (%)	52 (38)	30 (45)	34 (68)	8 (57)	58 (55)	13 (59)	1 (25)
PCyR, n (%)	14 (10)	8 (12)	3 (6)	0	9 (9)	2 (9)	0
MMR, n (%)	31 (23)	24 (36)	29 (58)	7 (50)	49 (47)	9 (41)	2 (50)
MR^4, n (%)	16 (12)	18 (27)	20 (40)	2 (14)	35 (33)	4 (18)	1 (25)
$MR^{4.5}$, n (%)	11 (8)	13 (19)	13 (26)	2 (14)	23 (22)	4 (18)	1 (25)
AP-CML	**N=41**	**N=24**	**N=16**	**N=2**	**N=36**	**N=6**	**N=0**
MaHR, n (%)	22 (54)	15 (63)	8 (50)	1 (50)	22 (61)	2 (33)	-
MCyR, n (%)	11 (27)	11 (46)	8 (50)	2 (100)	17 (47)	4 (67)	-
CCyR, n (%)	6 (15)	8 (33)	5 (31)	1 (50)	12 (33)	2 (33)	-
PCyR, n (%)	5 (12)	3 (13)	3 (19)	1 (50)	5 (14)	2 (33)	-
MMR, n (%)	5 (12)	4 (17)	3 (19)	1 (50)	6 (17)	1 (17)	-
MR^4, n (%)	1 (2)	3 (13)	0	0	3 (8)	0	-
$MR^{4.5}$, n (%)	1 (2)	3 (13)	0	0	3 (8)	0	-
BP-CML	**N=19**	**N=19**	**N=21**	**N=3**	**N=33**	**N=10**	**N=0**
MaHR, n (%)	4 (21)	8 (42)	7 (33)	0	12 (36)	3 (30)	-
MCyR, n (%)	1 (5)	6 (32)	7 (33)	0	10 (30)	3 (30)	-
CCyR, n (%)	1 (5)	5 (26)	5 (24)	0	7 (21)	3 (30)	-
PCyR, n (%)	0	1 (5)	2 (10)	0	3 (9)	0	-
Ph+ ALL	**N=4**	**N=6**	**N=15**	**N=7**	**N=19**	**N=8**	**N=1**
MaHR, n (%)	2 (50)	3 (50)	8 (53)	0	10 (53)	1 (13)	0
MCyR, n (%)	2 (50)	4 (67)	9 (60)	0	12 (63)	1 (13)	0
CCyR, n (%)	2 (50)	3 (50)	7 (47)	0	9 (47)	1 (13)	0
PCyR, n (%)	0	1 (17)	2 (13)	0	3 (16)	0	0

[a]Includes patients with no sequencing data

Table S7. Responses According to Specific Baseline Mutations

Mutations present in >1 patient at baseline in overall population		n Responses/N with mutation at baseline (%)								
		CP-CML N=267			AP-CML N=83		BP-CML N=62		Ph+ ALL N=32	
		MCyR	CCyR	MMR	MaHR	MCyR	MaHR	MCyR	MaHR	MCyR
P-loop Mutations	M244V	3/5 (60)	2/5 (40)	1/5 (20)	1/2 (50)	1/2 (50)	1/1 (100)	1/1 (100)	-	-
	L248V	1/2 (50)	1/2 (50)	1/2 (50)	1/1 (100)	1/1 (100)	-	-	-	-
	G250E	7/8 (88)	6/8 (75)	3/8 (38)	0/2 (0)	0/2 (0)	0/3 (0)	1/3 (33)	1/1 (100)	1/1 (100)
	Y253H	1/2 (50)	1/2 (50)	1/2 (50)	1/2 (50)	2/2 (100)	1/3 (33)	0/3 (0)	0/3 (0)	1/3 (33)
	E255K	6/8 (75)	6/8 (75)	4/8 (50)	1/3 (33)	0/3 (0)	1/6 (17)	1/6 (17)	0/1 (0)	0/1 (0)
	E255V	1/2 (50)	0/2 (0)	0/2 (0)	2/2 (100)	2/2 (100)	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)
Non-P-loop Mutations	L298V	0/1 (0)	0/1 (0)	0/1 (0)	1/1 (100)	1/1 (100)	-	-	-	-
	V299L	3/5 (60)	3/5 (60)	2/5 (40)	1/1 (100)	0/1 (0)	2/3 (67)	2/3 (67)	-	-
	F311L	1/1 (100)	1/1 (100)	0/1 (0)	1/1 (100)	1/1 (100)	-	-	0/1 (0)	0/1 (0)
	T315I	45/64 (70)	42/64 (66)	36/64 (56)	9/18 (50)	10/18 (56)	7/24 (29)	7/24 (29)	8/22 (36)	9/22 (41)
	F317I	-	-	-	-	-	-	-	2/2 (100)	2/2 (100)
	F317L	11/22 (50)	10/22 (45)	10/22 (45)	5/8 (63)	6/8 (75)	3/4 (75)	2/4 (50)	1/2 (50)	1/2 (50)
	M351T[a]	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	-	-	-	-
	E355A	1/2 (50)	1/2 (50)	1/2 (50)	0/1 (0)	0/1 (0)	-	-	-	-
	F359C	1/4 (25)	0/4 (0)	0/4 (0)	-	-	1/2 (50)	0/2 (0)	-	-
	F359I	3/4 (75)	1/4 (25)	0/4 (0)	-	-	-	-	-	-
	F359V	6/13 (46)	5/13 (38)	4/13 (31)	1/1 (100)	0/1 (0)	1/3 (33)	0/3 (0)	-	-
	H396R	1/5 (20)	1/5 (20)	2/5 (40)	0/1 (0)	0/1 (0)	-	-	-	-
	E450G	1/1 (100)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	-	-	-	-
	E459K	3/3 (100)	3/3 (100)	3/3 (100)	-	-	-	-	-	-

[a]Responses (complete cytogenetic response) in 2/2 CP-CML patients with M351T at baseline were observed in the phase 1 dose escalation trial[14]

Table S8. Response by prior therapy, AP-CML

Response by number of prior approved TKIs[a]	Total	R/I	T315I
1 Prior Approved TKI	***N=5***	***N=1***	***N=3***
MaHR	80%	100%	67%
MCyR	100%	100%	100%
CCyR	80%	100%	67%
MMR	40%	0%	33%
2 Prior Approved TKIs	***N=33***	***N=26***	***N=6***
MaHR	61%	65%	33%
MCyR	42%	35%	67%
CCyR	30%	23%	50%
MMR	24%	19%	33%
3 Prior Approved TKIs	***N=44***	***N=35***	***N=9***
MaHR	50%	49%	56%
MCyR	30%	29%	33%
CCyR	16%	17%	11%
MMR	11%	11%	11%
4 Prior Approved TKIs	***N=3***	***N=3***	***N=0***
MaHR	67%	67%	-
MCyR	67%	67%	-
CCyR	33%	33%	-
MMR	0%	0%	-

[a]Patients may have received other anti-cancer agents or investigational TKIs; This table includes the 2 patients who were unassigned to a cohort (T315I-negative at baseline and did not receive prior dasatinib or nilotinib)

Table S9. Response to ponatinib in myeloid and lymphoid BP-CML

	Myeloid BP-CML N=52	**Lymphoid BP-CML N=10**
MaHR	29%	40%
Any CyR[a]	37%	50%
MCyR	19%	40%
CCyR	15%	30%
[a]CCyR + PCyR + minor CyR + minimal CyR		

Table S10. Treatment-Related Adverse Events by Cohort

Preferred term	CP-CML		AP-CML		BP-CML		Ph+ ALL	
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=38	T315I N=24	R/I N=10	T315I N=22
Non-Hematologic	**% All Grades [% Grades 3/4]**							
Rash[b]	37 [3]	48 [6]	31 [3]	28 [6]	24 [3]	25 [4]	20 [10]	18 [0]
Dry skin	37 [2]	41 [2]	25 [2]	17 [0]	16 [3]	17 [0]	30 [0]	18 [0]
Abdominal pain	29 [8]	22 [5]	17 [6]	22 [0]	5 [0]	17 [4]	20 [0]	18 [9]
Headache	25 [2]	19 [2]	14 [0]	6 [0]	11 [0]	13 [4]	20 [0]	9 [0]
Lipase increased	24 [11]	14 [6]	15 [14]	11 [11]	18 [16]	4 [4]	20 [10]	5 [5]
Fatigue	18 [2]	22 [0]	17 [2]	28 [0]	16 [3]	4 [4]	0	14 [0]
Constipation	21 [1]	14 [2]	12 [2]	17 [0]	5 [0]	4 [0]	10 [0]	23 [5]
Myalgia	15 [1]	25 [2]	20 [0]	17 [0]	13 [0]	8 [0]	10 [0]	5 [0]
Arthralgia	18 [2]	14 [3]	18 [2]	22 [0]	13 [0]	13 [0]	0	5 [0]
Nausea	13 [<1]	16 [0]	11 [0]	11 [0]	16 [0]	25 [0]	0	5 [0]
ALT increased	12 [4]	9 [0]	12 [3]	11 [0]	5 [0]	13 [8]	0	5 [5]
Pancreatitis	7 [6]	8 [8]	11 [8]	0	5 [5]	4 [0]	0	0
Hypertension	9 [2]	9 [3]	6 [3]	11 [6]	3 [3]	0	10 [10]	0
AST increased	9 [2]	8 [0]	9 [5]	11 [0]	3 [0]	13 [4]	0	5 [5]
Blood amylase increased	7 [2]	2 [0]	8 [3]	6 [6]	8 [5]	0	10 [0]	0
Gamma-glutamyltransferase increased	5 [2]	2 [0]	8 [2]	11 [6]	5 [3]	0	0	0
Dyspnea	4 [2]	5 [0]	6 [0]	11 [0]	11 [3]	0	0	0
Cardiac failure	<1 [<1]	3 [2]	2 [2]	6 [6]	5 [5]	0	0	0
Hematologic								
Thrombocytopenia	47 [37]	23 [17]	49 [38]	17 [11]	37 [34]	13 [13]	10 [10]	9 [5]
Neutropenia	20 [17]	5 [5]	28 [28]	22 [22]	26 [18]	17 [17]	10 [10]	14 [14]
Anemia	12 [7]	3 [2]	17 [8]	17 [17]	26 [26]	17 [13]	10 [10]	18 [14]
White blood cell count decreased	5 [3]	0	9 [6]	6 [6]	0	0	0	5 [5]

Preferred term	CP-CML		AP-CML		BP-CML		Ph+ ALL	
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=38	T315I N=24	R/I N=10	T315I N=22
Pancytopenia	1 [1]	0	3 [2]	6 [6]	5 [5]	4 [4]	0	0
Febrile neutropenia	<1 [<1]	0	2 [2]	6 [6]	0	8 [8]	10 [10]	5 [5]

[a]Treatment-related events with a frequency ≥10% in the total study population (N=449) are presented, along with incidence of >1% in the total study population for grade 3/4 events.
[b]Combines the terms erythematous and papular rash.

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